108. The method of any one of claims 90-107, wherein said probe comprises recombinant nucleic acid.

109. The method of claim 108, wherein said recombinant nucleic acid is labeled.--

REMARKS

Reconsideration of this application is respectfully requested.

Claims 72-89 have been canceled. Claims 90-109 are new. Upon entry of the Amendment, claims 90-109 are pending in the application. No new matter enters by amendment. New claims 90-109 are derived from canceled claims 72-89 as follows:

Old Claim	New Claim
72	90
73	91
74	92, 93
75	92, 94
76	92, 95
77	92, 96
78	92, 97
79	92, 98
80	99
81	100
82	101, 102
83	101, 103
84	101, 104
85	101, 105
86	101, 106

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87	101, 107
88	108
89	109 .

Rejection under 35 U.S.C. § 112, first paragraph

Claims 72-89 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Office contends that the specification only provides a limited number of subgenomic HIV-2 clones, and that the specification fails to provide sufficient guidance pertaining to the nucleotide sequence of the inserts within these clones, with the exception of the LTR, *gag*, and *pol* [sic, *env*] genes described on pages 56-61 and Figures 6 and 7. The Office contends that nucleotide sequences or subgenomic clones corresponding to other regions of the viral genome are not described. The Office concludes that applicants have only provided a limited number of nucleic acid molecules that could be employed in the claimed methodology.

Applicants traverse the rejection. Applicants' specification teaches subgenomic clones of HIV-2, which together reconstitute **the complete HIV-2 ROD genome**:

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> pROD 27-5' and pROD 35, present on E. Coli HB 101, were deposited on November 21, 1986 with the CNCM . . . The complete HIV-2 ROD genome, the restriction map of which is seen in Figure 4, was reconstituted from pROD 35, linearized beforehand with EcoRI, and pROD 27-5'. . . .

(Specification at 26, lines 14-23.)

Therefore, contrary to the Office's assertions, applicants teach clones encompassing **the entire genome of HIV-2**. Consequently, the specification describes probes that are capable of hybridizing to **any** region of the HIV-2 genome using the claimed methodology.

Applicants' specification teaches restriction maps of the subgenomic clones, as well as nucleotide sequence information for LTR, *gag*, and *env* regions. (Specification at 56-61 and Figures 4-8.) Therefore, applicants submit that the specification conveys to the skilled artisan that applicants were in possession of a vast number of nucleic acid molecules, encompassing **the entire HIV-2 genome**, which could be used in the claimed methodology.

Applicants further submit that the claimed methods are broadly applicable, and that applicants have provided the requisite written description of the claimed **methods**. Applicants submit that the successful use of the methods is predictable.

Applicants are not required to disclose every species encompassed by their claims. In re Angstadt, 537 F.2d 498, 502-503, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). As in Angstadt, applicants have provided numerous working

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examples of the claimed methodology. See Id. As in Angstadt, the process described by applicants is not complicated, and one skilled in the art could merely substitute an HIV-2 specific probe in the claimed methodology. See Id. Applicants submit that, as in Angstadt, 35 U.S.C. § 112, first paragraph, does not require applicants to disclose every probe capable of working in the claimed invention.

Furthermore, the Federal Circuit has stated:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by the nucleotide sequence, falling within the scope of the genus or a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. . . .

University of California V. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 U.S.P.Q. 2d 1398, 1406 (Fed. Cir. 1997).

Although applicants have claimed methods in this application, applicants have provided nucleotide sequences of a representative number of HIV-2 specific probes, which will work in the claimed invention. Furthermore, applicants have recited a common structural feature of the members of the genus of probes, which will work in the claimed methodology. Specifically, applicants have recited that the probes hybridize to HIV-2ROD genomic DNA under hybridization conditions selected from the group consisting of 42°C below the melting temperature of the probe, 20°C below the melting temperature of the probe, and 3°C below the melting temperature of the probe. Accordingly,

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applicants submit that the requirements of the 35 U.S.C. § 112, first paragraph, have been fulfilled, and respectfully request withdrawal of the rejection.

Claims 72-89 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably enable one skilled in the art to make and/or use the invention commensurate in scope with the claims. The Office acknowledges that the skilled artisan could prepare probes from inserts released by restriction digest from those clones described in the specification for which sequence data is not available. Paper No. 25 at 3, last paragraph. However, the Office contends that the skilled artisan would not be capable of preparing HIV-2 specific probes corresponding to regions neither contemplated nor described by applicants (i.e. *pol, vif, vpr, vpx, tat, rev, nef*, or U5). The Office further asserts that it is not readily manifest how the skilled artisan could determine the T_m in the absence of information pertaining to the G/C content of the probe. The Office concludes that it would require undue experimentation for the skilled artisan to practice the claimed invention.

Applicants traverse the rejection. Applicants submit that the claimed **methods** are fully enabled by the specification, and that the skilled artisan could make and use the claimed invention without undue experimentation. As discussed above, applicants have described HIV-2 specific clones, which encompass **the entire genome of HIV-2**. Therefore, contrary to the Office's

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assertions, the skilled artisan would be capable of preparing HIV-2 specific probes corresponding to **the entire genome of HIV-2**.

Applicants have provided detailed methods for determining which probes can function in the claimed methods. The skilled artisan expects success in making and using the claimed invention. Since the successful use of the methods is predictable, the embodiments of the specification provide broad enablement, and no undue experimentation is required in their use.

Even a single embodiment may provide broad enablement in cases involving predictable factors. In re Cook, 439 F.2d 730, 734, 169 U.S.P.Q. 298, 301 (C.C.P.A. 1971). Applicants have provided numerous embodiments of the claimed invention. Applicants submit that, due to the predictability of the claimed invention and the embodiments provided by applicants, the scope of the claimed invention is fully enabled under 35 U.S.C. § 112.

Applicants further submit that the determination of the G/C content of a given probe would not require any undue experimentation. Applicants submit that, at the time the application was filed, the skilled artisan could have readily determined the G/C content of a probe using a variety of conventional techniques known in the art. As illustrated in Kirk, *Biochem J.* 105:673-677,1967 (Exhibit 1), Coene et al., *Eur J. Biochem* 150:475-479, 1985 (Exhibit 2), and Blake et al., *Biochim et Biophys Acta* 518:233-246,1978 (Exhibit 3), the skilled

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artisan could readily determine the G/C content of a DNA, as well as the melting temperature of a probe.

Kirk (Exhibit 1) describes a method for the determination of base composition (G/C content) of DNA by accurate measurement of the adenine/guanine ratio resulting from DNA hydrolysis. Kirk at 673.

Coene et al. (Exhibit 2) describes a procedure for the determination of G/C content of microquantities of DNA. Coene et al. at 475. Coene et al. also indicates that G/C content can be obtained from buoyant density or from the T_m of a DNA, and indicates that these determinations are easier and more sensitive procedures than the analysis of DNA hydrolysates. Id.

Blake et al. (Exhibit 3) describes a spectral method "[t]hat permits easy analysis for DNA base composition from the ratio of derivative melting curves obtained at 282 and 262 nm." Blake et al. at 233.

These articles indicate that, in order to practice the claimed invention, the G/C content and T_m of the probe could be readily determined without undue experimentation.

As discussed above, the level of skill in the art and the predictability of probe technology at the time the application was filed was such that the specification provides the skilled artisan with all that is necessary to make and use HIV-2 specific probes in the claimed invention. Therefore, the claimed invention can be practiced without undue experimentation. Accordingly, applicants respectfully request withdrawal of the rejection.

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The Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1561, 27 U.S.P.Q. 2d 1510, 1515 (Fed. Cir. 1993). In addition, M.P.E.P. § 2164.02 states:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. **Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.**

Furthermore, M.P.E.P. § 2164.04 states:

> While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. **This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact.** For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP 2164.06(a). **References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required. In re Marzocchi , 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.**

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Applicants submit that the Office has not met its burden since the Office has not explained why one skilled in the art could not make and use HIV-2 probes corresponding to the entire HIV-2 genome invention without undue experimentation. In fact, the Office has acknowledged that "[t]he skilled artisan would be capable of preparing probes from inserts released by restriction fragments from those clones described in the specification for which sequence data is not available." Paper No. 25 at 3. Since the specification describes clones encompassing the entire HIV-2 genome, for example in Figure 8, the Office's conclusion that "[t]he skilled artisan would not be capable of preparing probes corresponding to regions which are neither contemplated nor described by applicants. . . . " appears to be unsupportable.

In contravention of M.P.E.P. § 2164.02, no reasons have been advanced by the Office to establish that a person skilled in the art could not use the genus as a whole without undue experimentation. In contravention of M.P.E.P. § 2164.04, no findings of fact and no specific technical reasons have been provided by the Office to support its position. Rather, the Office appears to support the rejection primarily by reminding the applicants that the claimed invention encompasses a broad genus, including any HIV-2 specific probe, regardless of the nucleotide sequence from which it was derived. Applicants respectfully submit that this reasoning is insufficient to support a rejection under 35 U.S.C. § 112, first paragraph, and request withdrawal of the rejection.

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Rejection under 35 U.S.C. § 112, second paragraph

Claims 72-89 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter, which applicants regard as the invention. Applicants traverse the rejection.

The Office indicates that "Applicants' arguments have been considered but are deemed to be moot in view of the new issues raised below."

Applicants disagree with the Office's conclusion that applicants' arguments are "moot". Although applicants' arguments were not addressed to the "new issues" raised by the Office, applicants' arguments were relevant to the prior rejection of these claims under 35 U.S.C. § 112, second paragraph. Since the January 22, 1999, Office Action only refers to "new issues", applicants assume that the grounds for the prior rejection of these claims under 35 U.S.C. § 112, second paragraph, were overcome by applicants' arguments. Therefore, applicants arguments should not be considered "moot", but should properly be considered "persuasive".

The Office contends that the claims are incomplete for omitting essential positive method steps, such omission amounting to a gap between the steps, citing M.P.E.P. § 2173.05(q) and Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986).

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Applicants respectfully disagree. M.P.E.P. § 2173.05(q) indicates that attempts to claim a process without setting forth **any** steps involved in the process generally raise an issue of indefiniteness under 35 U.S.C. 112, second paragraph. However, applicants have not attempted to claim a process without setting forth **any** steps involved in the process. Rather, the method claims recite **multiple** steps involved in the process. Accordingly, applicants respectfully submit that the basis for this rejection is improper, and that the rejection should properly be withdrawn.

The Office contends that claim 72 recites vague and indefinite contact, washing, and detection steps. Specifically, the Office contends that the claim fails to describe the location of the sample, the formation of a hybridization complex comprising the HIV nucleic acid and probe of interest, the removal of non-specifically bound probe, and appropriate detection means. The Office also alleges that claim 80 fails to include those salient characteristics of the preparative method.

Applicants traverse the rejection. Applicants note that new claims 90 and 92 recite the steps of contacting a sample with an HIV-2 specific probe, washing the resulting hybrid, and detecting the hybrid. Applicants further note that new claims 99 and 101 recite the steps of preparing a nucleic acid insert, introducing the insert into a recombinant cloning vector, introducing the vector into a

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competent cellular host, and recovering the DNA recombinants. Applicants submit that these claims are not lacking any essential steps.

The steps, which the Office states are missing from claims 70 and 80, are not required to fulfill the requirements of 35 U.S.C. § 112, second paragraph. Rather, since the metes and bounds of the claimed invention are clearly ascertainable, the claims cannot be properly rejected as "vague and indefinite" under 35 U.S.C. § 112, second paragraph. In re Gardiner, 427 F.2d 786, 788, 166 U.S.P.Q. 138, 140 (C.C.P.A. 1970). Accordingly, applicants respectfully request withdrawal of the rejection.

The Office contends that the reference to a washing step "under conditions for hybridization" in claim 70 is confusing. Applicant disagree.

The skilled artisan would readily understand that this phrase referred to the conditions in part (a) of claim 70. Furthermore, new claims 90 and 92 do not recite this phrase. Instead, new claims 90 and 92 recite "washing the resulting hybrid under conditions selected from the group consisting of conditions of 42°C below the melting temperature of the probe, 20°C below the melting temperature of the probe, and 3°C below the melting temperature of the probe." Accordingly, applicants respectfully request withdrawal of the rejection.

The Office contends that claims 74 and 82 are confusing in their reference to a probe comprising nucleotides 1-380, wherein said nucleotides comprise the indicated sequences.

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As recommended by the Office, new claim 92 recites that the probe comprises an HIV-2 nucleic acid molecule "obtained from nucleotides 1-380 of the U3/R region" of HIV-2. Claim 93 recites that the probe is obtained from the recited nucleotide sequence. As recommended by the Office, new claim 101 recites that the insert is "obtained from nucleotides 1-380 of the U3/R region" of HIV-2. Claim 102 recites that the probe is obtained from the recited nucleotide sequence. Accordingly, applicants respectfully request withdrawal of the rejection.

The Office contends that claims 75-79 and 83-87 are confusing in their reference to an amino acid sequence comprising nucleotides of the indicated HIV-2 gene.

As recommended by the Office, new claims 92 and 101 indicate that the HIV-2 specific probes and inserts are obtained from the indicated nucleotides. Claims 94-98 and 103-107 recite that the probes and insert encode the recited amino acid sequence. Accordingly, applicants respectfully request withdrawal of the rejection.

The Office alleges that claims 79 and 87 are vague and indefinite in their reference to an amino acid sequence consisting of "Leu *** Gly". Specifically, the Office questions which amino acids should be included in this location, and which nucleotides encode this amino acid.

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Applicants traverse the rejection. Applicants submit that the meaning of "Leu *** Gly" in claims 98 and 107 is apparent from specification. On page 61 of the specification, an alignment of the recited amino acid sequence with a coding nucleotide sequence is illustrated. The skilled artisan recognizes that the *** corresponds to the nucleotides "TGA", which is a stop codon. Solely to expedite prosecution of the application, new claims 98 and 107 recite "wherein *** indicates a stop codon". Accordingly, applicants respectfully request withdrawal of the rejection.

Applicants respectfully submit that this application is now in condition for allowance. If the Examiner should disagree, he is invited to contact the undersigned to discuss any remaining issues.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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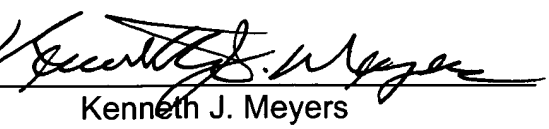
Dated: March 17, 1999

By: 

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